Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ursodeoxycholic acid Strides 250 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 250 mg of ursodeoxycholic acid.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard

White hard gelatin capsules (size '0') containing a white to off white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of primary biliary cholangitis (PBC) in patients without decompensated cirrhosis.
- Dissolution of radiolucent cholesterol gallstones not larger than 15 mm in diameter in patients with a functioning gallbladder and for whom surgical treatment is not indicated.
- Paediatric population: Hepatobiliary disorder associated with cystic fibrosis in children aged 6 years to less than 18 years

4.2 Posology and method of administration

Posology
There are no age restrictions on the use of Ursodeoxycholic acid Strides 250 mg Hard Capsules. For patients weighing less than 47 kg or patients who are unable to swallow Ursodeoxycholic acid Strides 250 mg Hard Capsules, other formulations are available (suspension).

The following daily dose is recommended for the various indications:

For treatment of primary biliary cholangitis (PBC)
Stage I-III
The daily dose is dependent on body weight and ranges from 3 to 7 capsules (12-16 mg ursodeoxycholic acid per kg of body weight).

During the first 3 months of treatment, ursodeoxycholic acid should be taken in divided doses throughout the day. If liver function improves, the total daily dose can be taken once daily in the evening.

Body weight (kg)	Daily dose (mg/kg body weight)	Ursodeoxycholic acid Strides 250 mg Hard Capsules			
		First 3 months			**Subsequently**
		Morning	Afternoon	Evening	Evening (once daily)
47 – 62	12 – 16	1	1	1	3
63 – 78	13 – 16	1	1	2	4
79 – 93	13 – 16	1	2	2	5
94 – 109	14 – 16	2	2	2	6
More than 110		2	2	3	7

Stage IV:
In combination with increased serum bilirubin levels (> 40 µg/L; conjugated), only half the normal dosage should initially be given (see dosage for stages I - III), (6 - 8 mg ursodeoxycholic acid per kg body weight per day, equivalent to about 2 to 3 ursodeoxycholic acid).

Thereafter, liver function should be closely monitored for several weeks (once every 2 weeks for 6 weeks). If there is no deterioration in liver function (AP, ALAT, ASAT, gamma-GT, bilirubin) and if no increased pruritus occurs, the dosage can be increased further to the usual level. However, liver function should again be closely monitored for several weeks. Once again, if there is no deterioration in liver function, the patient can be maintained at the normal dosage over the long term.

Patients with primary biliary cholangitis (stage IV) without increased serum bilirubin levels are allowed to receive the normal starting dose immediately (see dosage stages I - III).

However, close monitoring of liver function, as described above, is likewise applicable in such cases; treatment of primary biliary cholangitis will need to be regularly assessed on the basis of liver (laboratory) values and clinical findings.

Dissolution of gallstones:
Adults: Approx. 10mg ursodeoxycholic acid (UDCA) per kg body weight per day according to:
- up to 60 kg: 2 capsules
- 61-80 kg: 3 capsules
- 81-100 kg: 4 capsules
- above 100 kg: 5 capsules

Method of administration
For oral administration.

The capsules should be swallowed whole with some liquid in the evening before bedtime. Care should be taken to ensure that they are taken regularly.

Based on experience to date, the duration of the dissolution process with ursodeoxycholic acid is 6 months to 2 years, depending on the initial size of the stones. For a proper assessment of the therapeutic outcome, it is necessary, at the start of treatment, to accurately determine the size of the existing stones and subsequently to monitor them regularly, for example, every 3 to 4 months, via new X-rays and/or ultrasound scans.

In patients whose stones have not decreased in size after six months of treatment at the dosage stated, it is recommended that the biliary lithogenic index be determined via duodenal samples. If the bile has an index of > 1.0, it is unlikely that a favourable result can be obtained and it is better to consider a different form of treatment for gallstones. Treatment must be continued for 3 to 4 months after ultrasound follow-up has confirmed complete dissolution of the gallstones. Discontinuation of treatment for 3-4 weeks leads to a return of bile supersaturation and prolongs the overall duration of therapy. Discontinuation of treatment upon dissolution of the gallstones may be followed by a relapse.

Older people:
There is no evidence to suggest that any alteration in the adult dose is needed but the relevant precautions should be taken into account.

Paediatric population:
Children with cystic fibrosis aged 6 years to less than 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary.

4.3 Contraindications

Ursodeoxycholic acid should not be used in patients with:
- Hypersensitivity to active substance or to any of the excipients listed in section 6.1
- Acute inflammation of the gall bladder or biliary tract
- Occlusion of the biliary tract (occlusion of the common bile duct or a cystic duct)
- Frequent episodes of biliary colic
- Radio-opaque calcified gallstones
- Impaired contractility of the gall bladder

- Paediatric population: Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia

4.4 Special warnings and precautions for use

Ursodeoxycholic acid should be taken under medical supervision.

During the first 3 months of treatment, liver function parameters AST (SGOT), ALT (SGPT) and γ-GT should be monitored by the physician every 4 weeks, thereafter every 3 months. Apart from allowing for identification of responders and non-responders in patients being treated for primary biliary cholangitis, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage primary biliary cholangitis.

When used for dissolution of cholesterol gallstones:

In order to assess therapeutic progress and for timely detection of any calcification of the gallstones, depending on stone size, the gall bladder should be visualised (oral cholecystography) with overview and occlusion views in standing and supine positions (ultrasound control) 6-10 months after the beginning of treatment.

If the gall bladder cannot be visualised on X-ray images, or in cases of calcified gallstones, impaired contractility of the gall bladder or frequent episodes of biliary colic, ursodeoxycholic acid should not be used.

When used for treatment of advanced stage of primary biliary cholangitis:

In very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

Diarrhoea
If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.

Information on sodium content
This medicine contains less than 1 mmol sodium (23 mg) per capsule, i.e. is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Colestyramine, colestipol, antacids containing aluminium hydroxideand/or smectite
Ursodeoxycholic acid should not be administered concomitantly with colestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind ursodeoxycholic acid in the intestine and thereby inhibit its absorption and efficacy. Should the use of a preparation containing one of these substances be necessary, it must be taken at least 2 hours before or after ursodeoxycholic acid.

Ciclosporin
Ursodeoxycholic acid can increase the absorption of ciclosporin from the intestine. In patients receiving ciclosporin treatment, blood concentrations of this substance should therefore be checked by the physician and the ciclosporin dose adjusted if necessary.

Ciprofloxacin
In isolated cases ursodeoxycholic acid can reduce the absorption of ciprofloxacin.

Nitrendipine
Ursodeoxycholic acid has been shown to reduce the plasma peak concentrations (C_{max}) and the area under the curve (AUC) of the calcium antagonist nitrendipine.

Dapsone
An interaction with a reduction of the therapeutic effect of dapsone was also reported.

Cytochrome P450 3A enzymes
These observations together with in vitro findings could indicate a potential for ursodeoxycholic acid to induce cytochrome P450 3A enzymes. Controlled clinical trials have shown, however, that ursodeoxcholic acid does not have a relevant induction effect on cytochrome P450 3A enzymes.

Oestrogenic hormones and blood cholesterol lowering agents
Oestrogenic hormones and blood cholesterol lowering agents such as clofibrate may increase biliary lithiasis, which is a counter –effect to ursodeoxycholic acid used for dissolution of gallstones.

4.6 Fertility, pregnancy and lactation

Fertility
Women of childbearing potential should be treated only if they use reliable contraception: non-hormonal or low-oestrogen oral contraceptive measures are recommended. However, in patients taking ursodeoxycholic acid for dissolution of gallstones, effective non-hormonal contraception should be used, since hormonal oral contraceptives may increase biliary lithiasis.

Pregnancy
There are no adequate data on the use of ursodeoxycholic acid, particularly in the first trimester of pregnancy. Animal studies have provided evidence of a teratogenic effect during the early phase of gestation (see section 5.3, Toxicity to reproduction). Ursodeoxycholic acid must not be used during pregnancy unless clearly necessary.

The possibility of a pregnancy must be excluded before beginning treatment.

Breast-feeding
It is not known whether ursodeoxycholic acid passes into breast milk. Therefore, ursodeoxycholic acid should not be taken during lactation. If treatment with ursodeoxycholic acid is necessary, the infant should be weaned.

4.7 Effects on ability to drive and use machines

Ursodeoxycholic acid has no influence on ability to drive and use machines .

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following frequency data:
Very common (≥ 1/10)
Common (≥1/100 to < 1/10)
Uncommon (≥1/1,000 to < 1/100)
Rare (≥1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from available data)

System Organ Class	Frequency	Adverse Event
Gastrointestinal disorders	Common	Pasty stools or diarrhoea (reported from clinical trials)
	Very rare	Severe right upper abdominal pain (during the treatment of primary biliary cholangitis)
	Not known	Vomiting, nausea
Hepatobiliary disorders	Very rare	Calcification of gallstones, decompensation of hepatic cirrhosis (during therapy of the advanced stages of primary biliary cholangitis), which partially regressed after the treatment was discontinued.
	Not known	Increase of the serologic levels of alkaline phosphatase, γ-GT and bilirubin (in patients with an advanced stage of PBC).
Skin and subcutaneous disorders	Very rare	Urticaria
	Not known	Exacerbation of pruritus (upon the beginning of UDCA administration in patients with cirrhosis)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Diarrhoea may occur in cases of overdose. In general, other symptoms of overdose are unlikely because the absorption of ursodeoxycholic acid decreases with increasing dose and therefore more is excreted with the faeces. No specific counter-measures are necessary and the consequences of diarrhoea should be treated symptomatically with restoration of fluid and electrolyte balance.
However, ion-exchange resins may be useful to bind bile acids in the intestine. Liver function tests monitoring is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeuticgroup: Bile Acid Preparations, ATC Code: A05AA02

Mechanism of action
Bile acids are the most important components of bile and play a role in stimulating bile production. Bile acids are also important to keep cholesterol dissolved in bile. In healthy individuals, the ratio between cholesterol concentrations and bile acids in the gallbladder is such that cholesterol is kept dissolved for most of the day. Thus, no gallstones can form (bile is non-lithogenic). In patients with cholesterol stones in the gallbladder, this ratio has altered and the bile is supersaturated with cholesterol (bile is lithogenic). After some time, this may cause precipitation of cholesterol crystals and the formation of gallstones. Ursodeoxycholic acid can convert lithogenic bile into non-lithogenic bile and also gradually dissolve cholesterol gallstones.

Clinical efficacy and safety
Studies into the effect of ursodeoxycholic acid on cholestasis in patients with impaired biliary drainage and on clinical symptoms in patients with biliary cirrhosis have shown a rapid decline in cholestatic symptoms in the blood (as measured by increased levels of alkaline phosphatase (AP), gamma-GT and bilirubin) and pruritus, as well as decreased fatigue in most patients.

Paediatric population
Cystic fibrosis
From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at early stage of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to optimize treatment effectiveness.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination
Ursodeoxycholic acid occurs naturally in the body. When given orally it is rapidly and completely absorbed. It is 96-98% bound to plasma proteins and efficiently extracted by the liver and excreted in the bile as glycine and taurine conjugates. In the intestine some of the conjugates are deconjugated and reabsorbed. The conjugates may also be dehydroxylated to lithocholic acid, part of which is absorbed, sulphated by the liver and excreted via the biliary tract.

5.3 Preclinical safety data

Acute toxicity
Acute toxicity studies in animals have not revealed any toxic damage.

Chronic toxicity
Subchronic toxicity studies in monkeys showed hepatotoxic effects in the groups given high doses, including functional changes (e.g. liver enzyme changes) and morphological changes such as bile duct proliferation, portal inflammatory foci and hepatocellular necrosis. These toxic effects are most likely attributable to lithocholic acid, a metabolite of ursodeoxycholic acid, which in monkeys – unlike humans – is not detoxified. Clinical experience confirms that the described hepatotoxic effects are of no apparent relevance in humans.

Carcinogenic and mutagenic potential
At doses 3.2 times the recommended maximum human dose, based on body surface area, UDCA produced an increased incidence of pheochromocytomas of the adrenal medulla in

female rats in a life-span (2.5 year) study. Two-year studies in mice and rats revealed no evidence of carcinogenic potential. A tumour-promoting effect of the metabolite Lithocholic acid was observed when it was coadministered with a carcinogenic agent: The clinical relevance of these findings is unknown.

In vitro and in vivo genetic toxicology tests with ursodeoxycholic acid were negative.

The tests with ursodeoxycholic acid revealed no relevant evidence of a mutagenic effect.

Toxicity to reproduction
In studies in rats, tail malformations occurred after a dose of 2000 mg of ursodeoxycholic acid per kg of body weight. In rabbits, no teratogenic effects were found, although there were embryotoxic effects (from a dose of 100 mg per kg of body weight). Ursodeoxycholic acid had no effect on fertility in rats and did not affect peri-/post-natal development of the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Povidone (Kollidon K-30) (E1201)
Sodium Lauryl Sulphate (E487)
Maize Starch
Magnesium Stearate (E572)

Capsule Shell:
Gelatin (E441)
Titanium Dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Colourless PVC film with aluminium blister foil packed in cardboard cartons.

Capsules are available in packs of 20, 28, 30, 50, 56, 60, 100 and 120 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Strides Pharma (Cyprus) Limited
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Julia House

1st Floor
1066 Nicosia
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8 MARKETING AUTHORISATION NUMBER

PA22639/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st January 2014
Date of last renewal: 21st October 2018

10 DATE OF REVISION OF THE TEXT

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